At page 33, Applicants state

> Another embodiment of sustained release osmotic dosage forms of the invention includes drug dispersion-containing multiparticulates coated with a water-permeable membrane; the polymer may be dense, porous or asymmetric as described above. Such multiparticulates are prepared by, for example, melt-congealing from a spinning disk, extrusion/spheronization or fluid bed granulation, or by coating seed cores with a mixture of drug and a water-soluble polymer, as described above. [Page 33, lines 18-27]

Both of the above quotations from Applicants' specification disclose processes that include a step of making a melt. That in turn implies the use of meltable components and/or excipients. Similarly, Applicants' Example 9 discloses a melt congealing process in which an excipient (specifically COMPRITOL) is melted pursuant to providing controlled release multiparticulates. Thus, Applicants' respectfully submit that their specification well supports the term "meltable excipient". Reconsideration and withdrawal of the rejection is accordingly respectfully requested.

Claims 49-68 and 70-77 stand rejected for obviousness type double patenting over claims 1, 2, 4, 15-45, 47-49 and 51-67 of US patent 6,706,283 (hereinafter "'283"). The '283 patent issued out of the parent of the instant application.

The Examiner is respectfully requested to reconsider and withdraw the rejection. The touchstone of double patenting is the timewise extension of the claims in a prior issuing reference patent by a later issuing patent. Eli Lilly v. Barr Labs., Inc. 58 USPQ2d 1865, 1878 (Fed. Cir. 2001) ("The judicially-created doctrine of obviousness-type double patenting cements that legislative limitation [on the patentee's right to exclude] by prohibiting a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent.") The "later patent" here, of course, is the patent that will issue on the instant application. One means for overcoming an obviousness-type double patenting rejection is by submitting a terminal disclaimer to disclaim the terminal portion of the later-issuing patent, thereby avoiding any timewise extension of the earlier existing patent or application, '283 in the instant situation. A disclaimer that disclaims the terminal portion of any patent issuing on the instant application is not needed, however. That is because the (issued) double patenting reference, '283, will nominally expire twenty years from its date of filing, on the same date as any patent issuing on the instant application will expire, i.e., January 31, 2020. Because any patent issuing on the instant application will expire at the same time as '283, the instant application can provide no timewise extension to '283. Reconsideration and withdrawal of the double patenting rejection is accordingly respectfully requested.

Claims 49-57, 60-72, and 76-78 were rejected under 35 USC 103(a) over Ayer (US 5,035,897), in view of Baichwal (US 5,773,025).

The rejection is traversed on the basis that (1) Ayer is directed to a different problem than that solved by Applicants and (2) Ayer and Baichwal are not combinable because they teach away from each other. That is, to combine Baichwal with Ayer would defeat the purpose of Ayer.

Ayer is directed to a "critical need" for an osmotic dosage form that is applicable to soluble as well as insoluble drugs, that can deliver such drugs in a controlled or prolonged manner (column 1, lines 40-43), and that can administer a drug essentially independent of its chemical properties (column 1, lines 45-46). Ayer appears primarily interested in, *inter alia*, (1) preventing aqueous soluble drugs from being prematurely released (column 1, lines 26-27) and (2) preventing insoluble drugs from being delivered as intact solid forms (column 1, lines 35-37). Ayer solves his stated problem by formulating the drug into granules that can be used for both soluble and insoluble drugs.

In light of Ayer's statement that his invention is applicable to both aqueous soluble and insoluble drugs, Ayer is clearly unconcerned with improving the solubility of poorly soluble drugs *per se*; rather, he appears to be interested only in making controlled release granules that can be used with any drug regardless of its solubility. In summary each of Ayer's granules appear to be a miniature controlled release system for use independent of a drug's solubility characteristics.

Importantly, the Examiner has provided no basis from which one of ordinary skill in the art would conclude that Ayer is making a solid dispersion of a drug wherein at least a major portion of the drug is amorphous, as required by Applicants'. These fundamental elements are all missing from Ayer, which is not unexpected since Ayer was not interested in improving solubility generally. The Examiner noted that Ayer discloses spray drying, and thereby appeared to be contending either that the Ayer was making dispersions or that Ayer's drug is amorphous, but it is not understood how or why the Examiner concluded this merely from the fact that Ayer merely mentioned spray drying. Attachment 1 hereto (Remington: The Science And Practice Of Pharmacy, 20th Edition, Edited By Alfonso R. Gennaro, Chapter 37, pages 681-682) in fact makes the following statement on page 681 (relevant text is highlighted) in respect of powders produced by spray drying:

> The particles produced are aggregates of primary particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal.

Thus, as Remington confirms, a spray-dried drug can be either crystalline or amorphous, meaning that the fact that spray drying is disclosed in a reference does not mean that the spray dried product is necessarily amorphous. Ayer does not otherwise disclose how to make a dispersion in which a majority of the drug is amorphous.

Baichwal discloses sustained release oral solid dosage forms comprising agglomerated particles of a medicament in amorphous form, a gelling agent, an ionizable gel strength enhancing agent, and an inert diluent. Baichwal appeared to be cited for its disclosure of using active medicaments in amorphous form and/or for his statement that an insoluble medicament is rendered more bioavailable by dispersing it into a carrier to form a "solid solution" or a "solid dispersion" (column 6, lines 49-57). It is, at least in part, Baichwal's disclosure relating to rendering a drug bioavailable that renders the combination of Ayer and Baichwal untenable, in fact and in law.

In fact, Ayer clearly states that his dosage form is designed to achieve administration of a drug **independent of its chemical properties** (column 1, lines 45-46, emphasis supplied), solubility being such a property. Ayer reinforces that very point by citing the critical need for "...a dosage form that can deliver both soluble and insoluble drugs at a controlled rate to provide...drug in either instance for its beneficial effects over a prolonged time span..." (column 3, lines 40-45). In distinct contrast, Baichwal's purpose in respect of certain of his preferred embodiments is to provide improved solubility characteristics for insoluble medicaments (column 6, lines 49-57). One of ordinary skill would not combine a reference whose purpose is to make a dosage form that operates independent of solubility (Ayer) with a reference whose purpose is to improve solubility. The combination is simply not tenable because Ayer's purpose, making a dosage form that functions independent independent of solubility, is contrary to the purpose of improving solubility specifically expressed in Baichwal. The two references are simply at cross purposes.

In law, the Federal Circuit Court has held that it is error for the USPTO to reject a claimed invention as an obvious combination of the teachings of two prior art references when the prior art provided no teaching, suggestion or incentive supporting the combination. "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination." *In re Bond*, 910 F2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990); *See also ACS Hospital Systems, Inc. v. Montefiori Hospital*, 732 F.2d 1572, 1577 (Fed. Cir. 1984). The Federal Circuit Court has further held that, in questions of obviousness, one "cannot pick and choose among the individual elements of assorted prior art references to recreate a claimed invention." *SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988). These holdings are all the more significant in respect of the instant situation in which

Ayer and Baichwal not only fail to supply any such suggestion, motivation or, incentive, but that actually teach away from each other.

Claims 58, 59, and 73-75 were rejected under 35 USC 103(a) as being unpatentable over Ayer and Baichwal and Kigoshi, US 6,254,889. Ayer and Baichwal were relied on for the reasons previously given by the Examiner. Kigoshi was cited apparently to fill in additional missing elements present in the rejected claims but not present in Ayer and/or Baichwal.

The rejection is traversed on the basis that, regardless of what Kigoshi allegedly discloses, it does nothing to remedy the fatal defects of the Ayer/Baichwal combination. Applicants' discussion from above in respect of Ayer and Baichwal is incorporated by reference in this respect. The combination of Ayer and Baichwal is untenable, both legally and factually, for all of the reasons cited above. The disclosure by Kigoshi of additional elements present in the dependent claims rejected over the Ayer-Baichwal-Kigoshi reference combination does nothing to make the Ayer/Baichwal combination any more tenable.

Withdrawal of all of the obviousness rejections over Ayer, Baichwal and Kigoshi is accordingly respectfully requested.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

Date: May 2, 2005

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Current claim summary

1- 48 (Canceled)

49. (currently amended) A controlled release dosage form, comprising:

(a) a core comprising an osmotic agent and a low solubility drug in the form of a solid dispersion of said drug in a dispersion polymer, at least a major portion of said drug being amorphous, wherein said drug in said solid dispersion exhibits amorphous character in at least one of x-ray diffraction analysis ~~and~~ or differential scanning calorimetry;

(b) a water-permeable coating around said core having at least one delivery port therein, said coating controlling the influx of water to said core from an aqueous environment of use to cause extrusion of at least a portion of said core through said at least one delivery port to said aqueous environment of use, said coating being non-dissolving and non-eroding during release of said drug;

wherein said dispersion polymer is a cellulosic polymer.

50. (previously presented) The dosage form of claim 49 wherein substantially all of said drug is amorphous.

51. (previously presented) The dosage form of claim 49 wherein said solid dispersion is homogeneous.

52. (previously presented) The dosage form of claim 49 further comprising an osmotically effective solute.

53. (previously presented) The dosage form of claim 49 wherein said osmotic agent and said solid dispersion are in respective discrete portions of said dosage form.

54. (previously presented) The dosage form of claim 53 wherein said osmotic agent is in a first layer and said solid dispersion is in a second layer.

55. (previously presented) The dosage form of claim 49 wherein said osmotic agent comprises a water-swellable hydrophilic polymer that is separate from said dispersion polymer.

56. (previously presented) The dosage form of claim 55 wherein said water-swellable hydrophilic polymer is selected from the group consisting of hydrophilic vinyl and acrylic polymers, polysaccharide alginates, poly(ethylene oxide), polyethylene glycol, polypropylene glycol, poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinyl pyrrolidone, crosslinked polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl pyrrolidone/polyvinyl alcohol copolymers, vinyl acetate, hydrophilic polyurethanes containing large polyethylene oxide blocks, carrageenan, hydroxethyl-cellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose, carboxymethylcellulose, carboxyethylcellulose, sodium alginate, polycarbophil, gelatin, xanthan gum, sodium croscarmellose, and sodium starch glycolate.

57. (previously presented) The dosage form of claim 49 wherein said solid dispersion is formed by spray-drying said low-solubility drug and said dispersion polymer together in a solvent.

58. (previously presented) The dosage form of claim 49 wherein said dispersion polymer is selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, and carboxymethylethylcellulose.

59. (previously presented) The dosage form of claim 49 wherein said dispersion polymer is hydroxypropylmethyl cellulose acetate succinate.

60. (previously presented) The dosage form of claim 49 wherein said dosage form provides an AUC in a use environment that is at least 1.25-fold that of a control dosage form comprising an identical dosage form containing an equivalent quantity of undispersed drug.

61. (previously presented) The dosage form of claim 49 wherein said dosage form is dosed orally to a mammal, said dosage form provides an AUC in drug concentration in the blood that is at least 1.25-fold that of a control dosage form comprising an identical dosage form except containing an equivalent quantity of undispersed drug.

62. (previously presented) The dosage form of claim 49 wherein said drug is selected from the group consisting of an anti-hypertensive, and antianxiety agent,

an anticlotting agent, a blood glucose-lowering agent, a decongestant, an antihistamine, an antitussive, an anti-inflammatory, an anti-atherosclerotic agent, an antipsychotic agent, a cognitive enhancer, a cholesterol-reducing agent, an antiobesity agent, an autoimmune disorders agent, a hypnotic agent, an anti-Parkinsonism agent, an antibiotic, an antiviral agent, an anti-impotence agent, an anti-neoplastic, a sedative, a barbituate, a nutritional agent, a beta-blocker, an emetic, an anti-emetic, a diuretic, an anticoagulant, a cardiotonic, an androgen, a corticoid, an anabolic agent, an anti-depression agent, an anti-infective agent, a coronary vasodilator, a carbonic anhydrase inhibitor, an antifungal, an antiprotozoal, a gastrointestinal agent, a dopaminergic agent, an anti-Alzheimer's Disease agent, an anti-ulcer agent, a platelet inhibitor, and a glycogen phosphorylase inhibitor.

63. (currently amended) A controlled release dosage form, comprising:

(a) a plurality of multiparticulates, each of said multiparticulates comprising a core surrounded by a water permeable coating;

(b) said core comprising a low-solubility drug in the form of a solid dispersion of said drug in a dispersion polymer, at least a major portion of said drug being amorphous, wherein said drug in said solid dispersion exhibits amorphous character in at least one of x-ray diffraction analysis ~~and~~ or differential scanning calorimetry; and

(c) said core further comprising an osmotic agent separate from said dispersion polymer.

64. (previously presented) The dosage form of claim 63 wherein said solid dispersion is in the form of particles distributed throughout said core.

65. (previously presented) The dosage form of claim 63 wherein said solid dispersion comprises a coating surrounding a seed core.

66. (previously presented) The dosage form of claim 63 further comprising a meltable excipient.

67. (previously presented) The dosage form of claim 65 wherein said seed core comprises a meltable excipient.

68. (previously presented) The dosage form of claim 67 wherein said seed core comprises said osmotic agent.

69. (previously presented) The dosage form of claim 63 wherein said core is formed by melt-congealing from a spinning disk.

70. (previously presented) The dosage form of claim 63 wherein said osmotic agent comprises a water-swellable polymer that is separate from said dispersion polymer.

71. (previously presented) The dosage form of claim 68 wherein said water-swellable polymer is selected from the group consisting of hydrophilic vinyl and acrylic polymers, polysaccharide alginates, poly(ethylene oxide), polyethylene glycol, polypropylene glycol, poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinyl pyrrolidone, crosslinked polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl pyrrolidone/polyvinyl alcohol copolymers, vinyl acetate, hydrophilic polyurethanes containing large polyethylene oxide blocks, carrageenan, hydroxethyl-cellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose, carboxymethylcellulose, carboxyethylcellulose, sodium alginate, polycarbophil, gelatin, xanthan gum, sodium croscarmellose, and sodium starch glycolate.

72. (previously presented) The dosage form of claim 63 wherein said dispersion polymer is selected from the group consisting of:

(a) ionizable cellulosic polymers;

(b) nonionizable cellulosic polymers; and

(c) vinyl polymers and copolymers having substituents selected from the group consisting of hydroxyl, alkylacyloxy and cyclicamido.

73. (previously presented) The dosage form of claim 72 wherein said dispersion polymer comprises hydroxypropylmethyl-cellulose, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, carboxymethylethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, and copolymers of polyvinyl pyrrolidone and polyvinyl alcohol.

74. (previously presented) The dosage form of claim 72 wherein said dispersion polymer is selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose acetate

phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, and carboxymethylethylcellulose.

75. (previously presented) The dosage form of claim 63 wherein said dispersion polymer is hydroxypropylmethyl cellulose acetate succinate.

76. (previously presented) The dosage form of claim 63 wherein said solid dispersion is formed by spray-drying said low-solubility drug and said dispersion polymer together in a solvent.

77. (previously presented) The dosage form of claim 63 wherein said drug is selected from the group consisting of an anti-hypertensive, and antianxiety agent, an anticlotting agent, a blood glucose-lowering agent, a decongestant, an antihistamine, an antitussive, an anti-inflammatory, an anti-atherosclerotic agent, an antipsychotic agent, a cognitive enhancer, a cholesterol-reducing agent, an antiobesity agent, an autoimmune disorders agent, a hypnotic agent, an anti-Parkinsonism agent, an antibiotic, an antiviral agent, an anti-impotence agent, an anti-neoplastic, a sedative, a barbituate, a nutritional agent, a beta-blocker, an emetic, an anti-emetic, a diuretic, an anticoagulant, a cardiotonic, an androgen, a corticoid, an anabolic agent, an anti-depression agent, an anti-infective agent, a coronary vasodilator, a carbonic anhydrase inhibitor, an antifungal, an antiprotozoal, a gastrointestinal agent, a dopaminergic agent, an anti-Alzheimer's Disease agent, an anti-ulcer agent, a platelet inhibitor, and a glycogen phosphorylase inhibitor.

78. (previously presented) The dosage form of claim 63 wherein said core, when exposed to an aqueous use environment, swells and ruptures said coating.

ATTACHMENT 1

20 TH EDITION

Remington: The Science and Practice of Pharmacy

ALFONSO R GENNARO
Chairman of the Editorial Board
and Editor

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Twentieth Edition—2000

Published in the 180th year of the
PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

Editor: Daniel Limmer
Managing Editor: Matthew J. Hauber
Marketing Manager: Anne Smith

Lippincott Williams & Wilkins

351 West Camden Street
Baltimore, Maryland 21201-2436 USA

227 East Washington Square
Philadelphia, PA 19106

Printed in the United States of America

Entered according to Act of Congress, in the year 1885 by Joseph P Remington, in the Office of the Librarian of Congress, at Washington DC

Library of Congress Catalog Card Information is available
ISBN 0-683-306472

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02 03 04
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CHAPTER 37

Powders

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Powders are encountered in almost every aspect of pharmacy, both in industry and in practice. Drugs and other ingredients, when they occur in the solid state in the course of being processed into a dosage form, usually are in a more or less finely divided condition. Frequently, this is a powder whose state of subdivision is critical in determining its behavior both during processing and in the finished dosage form. Apart from their use in the manufacture of tablets, capsules, and suspensions, powders also occur as a pharmaceutical dosage form. Although the use of powders as a dosage form has declined, the properties and behavior of finely divided solid materials are of considerable importance in pharmacy.

This chapter is intended to provide an introduction to the fundamentals of powder mechanics and the primary means of powder production and handling. The relationships of the principles of powder behavior to powders as dosage forms are discussed.

PRODUCTION METHODS

Molecular Aggregation

PRECIPITATION AND CRYSTALLIZATION

The precipitation and crystallization processes are fundamentally similar and depend on achieving three conditions in succession: a state of supersaturation (super cooling in the case of crystallization from a melt), formation of nuclei, and growth of crystals or amorphous particles.

Supersaturation can be achieved by evaporation of solvent from a solution, cooling of the solution if the solute has a positive heat of solution, production of additional solute as a result of a chemical reaction, or a change in the solvent medium by addition of various soluble secondary substances. In the absence of seed crystals, significant supersaturation is required to initiate the crystallization process through formation of nuclei. A nucleus is thought to consist of from 10 to a few hundred molecules having the spatial arrangement of the crystals that will be grown ultimately from them.

Such small particles are shown by the Kelvin equation to be more soluble than large crystals; therefore, they require supersaturation, relative to large crystals, for their formation and subsequent growth. It is a gross oversimplification to assume that, for a concentration gradient of a given value, the rate of crystallization is the negative of the rate of dissolution. The latter is generally somewhat greater.

Depending on the conditions of crystallization, it is possible to control or modify the nature of the crystals obtained. When polymorphs exist, careful temperature control and seeding with the desired crystal form are often necessary. The habit or shape of a given crystal form often highly depends on impurities in solution, pH, rate of stirring, rate of cooling, and the solvent. Very rapid rates of crystallization can result in impurities being included in the crystals by entrapment.

SPRAY-DRYING

Atomization of a solution of one or more solids via a nozzle, spinning disk, or other device, followed by evaporation of the solvent from the droplets is termed *spray-drying*. The nature of the powder that results is a function of several variables, including the initial solute concentration, size distribution of droplets produced, and rate of solvent removal. The weight of a given particle is determined by the volume of the droplet from which it was derived and by the solute concentration. The particles produced are aggregates of primary particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal. This approach to the powdered state provides the opportunity to incorporate multiple solid substances into individual particles at a fixed composition, independent of particle size, and avoiding difficulties that can arise in attempting to obtain a uniform mixture of several powdered ingredients by other procedures.

Particle-Size Reduction

Comminution in its broadest sense is the mechanical process of reducing the size of particles or aggregates. Thus, it embraces a wide variety of operations including cutting, chopping, crushing, grinding, milling, micronizing, and trituration, which depend primarily on the type of equipment employed. The selection of equipment in turn is determined by the characteristics of the material, the initial particle size and the degree of size reduction desired. For example, very large particles may require size reduction in stages simply because the equipment required to produce the final product will not accept the initial feed, as in crushing prior to grinding. In the case of vegetable and other fibrous material, size reduction generally must be, at least initially, accomplished by cutting or chopping.

Chemical substances used in pharmaceuticals, in contrast, generally need not be subjected to either crushing or cutting operations prior to reduction to the required particle size. How-

ever, these materials do differ considerably in melting point, brittleness, hardness, and moisture content, all of which affect the ease of particle-size reduction and dictate the choice of equipment. The heat generated in mechanical grinding, in particular, presents problems with materials that tend to liquefy or stick together and with the thermolabile products that may degrade unless the heat is dissipated by use of a flowing stream of water or air. The desired particle size, shape, and size distribution also must be considered in the selection of grinding or milling equipment. For example, attrition mills tend to produce spheroidal, more free-flowing particles than do impact-type mills, which yield more irregular-shaped particles.

FRACTURE MECHANICS

Reduction of particle size through fracture requires application of mechanical stress to the material to be crushed or ground. Materials respond to stress by yielding, with consequent generation of strain. Depending on the time course of strain as a function of applied stresses, materials can be classified according to their behavior over a continuous spectrum ranging from brittle to plastic. In the case of a totally brittle substance, complete rebound would occur on release of applied stress at stresses up to the yield point, where fracture would occur. In contrast, a totally plastic material would not rebound nor would it fracture.

The vast majority of pharmaceutical solids lie somewhere between these extremes and thus possess both elastic and viscous properties. Linear and, to a lesser extent, nonlinear viscoelastic theory has been developed well to account for quantitatively and explain the simultaneous elastic and viscous deformations produced in solids by applied stresses.

The energy expended by comminution ultimately appears as surface energy associated with newly created particle surfaces, internal free energy associated with lattice changes, and as heat. Most of the energy expressed as heat is consumed in the viscoelastic deformation of particles, friction, and in imparting kinetic energy to particles. Energy is exchanged among these modes and some is, of course, effective in producing fracture. It has been estimated that 1% or less of the total mechanical energy used is associated with newly created surface or with crystal lattice imperfections.

Although the grinding process has been described mathematically, the theory of grinding has not been developed to the point where the actual performance of the grinding equipment can be predicted quantitatively. However, three fundamental laws have been advanced:

Kick's Law—The work required to reduce the size of a given quantity of material is constant for the same reduction ratio regardless of the original size of the initial material.

Rittinger's Law—The work used for particulate size reduction is directly proportional to the new surface produced.

Bond's Law—The work used to reduce the particle size is proportional to the square root of the diameter of the particles produced.

In general, however, these laws have been useful only in providing trends and qualitative information on the grinding process. Usually laboratory testing is required to evaluate the performance of particular equipment. A work index, developed from Bond's Law, is a useful way of comparing the efficiency of milling operations.[1] A grindability index, which has been developed for a number of materials, also can be used to evaluate mill performance.[2]

A number of other factors also must be considered in equipment selection. Abrasion or mill wear is an important factor in the grinding of hard materials, particularly in high-speed, close-clearance equipment (eg, hammer mills). In some instances mill wear may be so extensive as to lead to highly contaminated products and excessive maintenance costs that make the milling process uneconomical. Hardness of the material, which often is related to abrasiveness, also must be considered. This usually is measured on the Moh's scale.

Qualitatively, materials from 1 to 3 are considered as soft and from 8 to 10 as hard. Friability (ease of fracture) and fibrousness can be of equal importance in mill selection. Fibrous materials, such as plant products, require a cutting or chopping action and usually cannot be reduced in size effectively by pressure or impact techniques. A moisture content above about 5% will in most instances also create a problem and can lead to agglomeration or even liquefaction of the milled material. Hydrates often will release their water of hydration under the influence of a high-temperature milling process and thus may require cooling or low-speed processing.

METHODS AND EQUIPMENT

When a narrow particle-size distribution with a minimum of fines is desired, closed-circuit milling is advantageous. This technique combines the milling equipment with some type of classifier (see *Particle-Size Measurement and Classification*). In the simplest arrangement, a screen is used to make the separation, and the oversize particles are returned to the mill on a continuous basis while the particles of the desired size pass through the screen and out of the grinding chamber. Over-milling, with its subsequent production of fines, thereby is minimized. Equipment also has been designed to combine the sieving and milling steps into a single operation (see *Centrifugal-Impact Mills and Sieves*).

To avoid contamination or deterioration, the equipment used for pharmaceuticals should be fabricated of materials that are chemically and mechanically compatible with the substance being processed. The equipment should be easy to disassemble for cleaning to prevent cross-contamination. Dust-free operation, durability, simplified construction, and operation and suitable feed and outlet capacities are additional considerations in equipment selection.

Although there is no rigid classification of large-scale comminution equipment, it generally is divided into three broad categories based on feed and product size:

1. *Coarse crushers* (eg, jaw, gyratory, roll, and impact crushers).
2. *Intermediate grinders* (eg, rotary cutters, disk, hammer, roller, and chaser mills).
3. *Fine grinding mills* (eg, ball, rod, hammer, colloid, and fluid-energy mills; high-speed mechanical screen and centrifugal classifier).

Machines in the first category are employed ordinarily where the size of the feed material is relatively large, ranging from 1½ to 60 inches in diameter. These are used most frequently in the mineral crushing industry and will not be considered further. The machines in the second category are used for feed materials of relatively small size and provide products that fall between 20- and 200-mesh. Those in the third category produce particles, most of which will pass through a 200-mesh sieve, although often the particle size of the products from fine grinding mills is well into the micron range.

The comminution effect of any given operation can be described mathematically in terms of a matrix whose elements represent the probabilities of transformation of the various-size particles in the feed material to the particle sizes present in the output. The numerical values of the elements in the transition matrix can be determined experimentally and the matrix serves to characterize the mill. Matrices of this type are frequently a function of feed rate and feed particle-size distribution but are useful in predicting mill behavior. Multiplication of the appropriate comminution matrix with the feed-size distribution line-matrix yields the predicted output-size distribution.

INTERMEDIATE AND FINE GRINDING MILLS

The various types of comminuting equipment in this class generally employ one of three basic actions or, more commonly, a combination of these actions.